EPA Registration Division Contact: Mr. J.A. Tompkins, 703-305-5697

1. E.I. du Pont de Nemours and Company

PP No. (to be assigned)

EPA has received a pesticide petition (PP No. to be assigned) from E.I. du Pont de Nemours and Company, DuPont Crop Protection, Laurel Run Plaza, P.O. Box 80038, Wilmington, DE 19880-0038, proposing pursuant to section 408 (d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 346a (d), to amend 40 CFR Part 180.439 by establishing a tolerance for residues of the herbicide thifensulfuron methyl {Methyl-3-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino] carbonyl] amino] sulfonyl] -2-thiophenecarboxylate} in or on the following raw agricultural commodities: Rice grain at 0.05 ppm, Rice straw at 0.05 ppm, Grain sorghum grain at 0.05 ppm, Grain sorghum forage at 0.05 ppm, and Grain sorghum stover at 0.05 ppm. EPA has determined that the petition contains data or information regarding the elements set forth in section 408 (d) (2) of the FFDCA; however, EPA has not fully evaluated the sufficiency of the submitted data at this time or whether the data supports granting of the petition. Additional data may be needed before EPA rules on the petition.

A. Residue Chemistry

1a. Plant Metabolism

The qualitative nature of the residues of thifensulfuron methyl in plants is adequately understood. Three plant metabolism studies – in wheat, corn, and soybeans - were conducted. Crops were treated with [thiophene-2-^{14}C] and [triazine-2-^{14}C] thifensulfuron methyl via direct foliage application. [^{14}C] Thifensulfuron methyl was rapidly metabolized in all three crops, and the nature of the metabolites was essentially the same regardless of the crop. In all three crops, metabolism involved cleavage of the urea bridge, metabolism (O-demethylation) of the methoxy group on the triazine ring, and hydrolysis of the methyl ester group on the thiophene ring. Minor differences in the formation and decline of short-lived intermediates were observed, however these differences were not environmentally significant because of the low levels of these intermediate metabolites in the crops.

Metabolism studies conducted with ^{14}C-thifensulfuron methyl on wheat (at a rate of approximately 28-30 g ai/acre) under field conditions showed no significant residues of thifensulfuron methyl or its degradation products (i.e., all less than 0.01 ppm) in wheat grain at maturity. Mature straw total residues were 0.45 to 0.80 ppm for the triazine and thiophene-labeled tests, respectively. Metabolites in wheat straw included thifensulfuron methyl, thifensulfuron acid, O-demethyl thifensulfuron methyl, 2-ester-3-sulfonamide, 2-acid-3-sulfonamide, triazine urea, triazine amine, and O-demethyl triazine amine. Complete breakdown of [^{14}C]thifensulfuron methyl and/or metabolites resulting in re-incorporation of the radiolabel into natural plant constituents (e.g., sugars) was also observed. No single metabolite was greater than 0.06 ppm in the mature wheat straw.

Metabolism studies with [^{14}C]thifensulfuron methyl were conducted (at a rate of approximately 14 g ai/acre) in field grown corn. There were no detectable residues of thifensulfuron methyl or its transformation products in corn grain (i.e., all less than 0.01 ppm) or foliage (i.e., all less than 0.02 ppm) at maturity. Analysis of non-mature foliar samples showed rapid and extensive metabolism of thifensulfuron methyl. Among the residues detected were thifensulfuron methyl, 2-acid-3-sulfonamide, triazine urea, triazine amine, O-demethyl triazine urea, and O-demethyl triazine amine. Thifensulfuron acid and 2-ester-3-sulfonamide, which are metabolites seen in other plant metabolism studies (wheat and soybean), were not detected, but were most likely transient intermediates (both plausible precursors to 2-acid-3-sulfonamide) in the corn plants.

Metabolism studies were conducted with soybeans under greenhouse conditions (at rates of 3 and 6 g ai per acre). There were no detectable residues (i.e., all less than 0.01 ppm) in the beans or pods at either rate at final harvest. Analysis of non-mature foliar samples showed extensive metabolism of thifensulfuron methyl. Residues detected included thifensulfuron methyl, thifensulfuron acid, 2-ester-3-sulfonamide, 2-acid-3-sulfonamide, triazine amine, and O-demethyl triazine amine.

1b. Confined Rotational Crop Studies

Two different crop rotation scenarios were investigated, one involving a bare ground application, the other with a cover crop (wheat). No significant difference in metabolic profile was observed in the rotated crops (beets, peas, and sunflowers) under either scenario. No thifensulfuron methyl (i.e., <0.01 mg/kg) was detected in any food or feed item from any of the rotated crops.

A confined greenhouse crop rotation study (following application to bare soil) was conducted with thiophene-^{14}C thifensulfuron methyl by planting beets, peas, and sunflowers at either a 30 or 120 day treatment-to-planting interval. The application rate used was 35 - 38 g ai/acre. Total soil residue levels at planting were low, 0.01 – 0.02 mg/kg for both the 30- and 120-day aging periods. Levels of thifensulfuron methyl at planting accounted for <0.01 mg/kg at the end of each aging period. There were no significant residues (i.e., all less than 0.005 ppm) in food items (beet root, peas, sunflower seeds) in crops planted 30 or 120 days following soil treatment. There were minor detectable residues (0.02 to 0.05ppm) in animal feed items (beet foliage and sunflower foliage). Thifensulfuron methyl was only identified (<0.01 ppm) in sunflower foliage 73 days after treating the soil; other minor components observed were polar.

A confined greenhouse crop rotation study (following triazine-^{14}C thifensulfuron methyl treated wheat) was conducted using beet root, peas, pea pods, and sunflower as following crops. The study used an application rate of 15 g ai/acre, and a 45 or 75 day treatment-to-planting interval. At the end of the 45- and 75-day aging periods (after incorporation of the cover crop), soil residue levels were 0.01 – 0.02 mg thifensulfuron methyl equivalents per kg of soil. Thifensulfuron methyl was not detected in the soil after 45 days; triazine urea was the principal soil component at the 45- and 75-day planting interval. There were no substantial residues (i.e., all less than 0.01 ppm) in food items (beet root, peas, pea pods, sunflower (seeds and heads) in crops

planted 45 or 75 days following treated wheat incorporation into the soil. There were minor detectable residues in animal feed items. Sunflower and pea foliage contained 0.04 – 0.05 ppm and 0.01 - 0.02 ppm for the 45 and 75 day planting, respectively. Small amounts of triazine amine (< 0.03 ppm), triazine urea, and O-demethyl triazine amine were identified in these fractions.

The proposed use of thifensulfuron methyl on grain sorghum and rice is supported by the wheat and field corn metabolism studies.

2. Analytical Methods

For wheat, barley, and soybeans, the analytical methods use liquid chromatography and a photoconductivity detector for thifensulfuron methyl. Coupled with extraction, cleanup and isolation procedures, these methods provide a means of determining thifensulfuron methyl in soybeans, and in wheat and barley straw, with a detection limit of 50 ppb (50 ng/g), based on a 5-gram sample (soybeans) or a 10-gram sample (wheat and barley).

For corn forage and whole ears, the analytical method used liquid chromatography and a photoconductivity detector for thifensulfuron methyl. Coupled with extraction, cleanup and isolation procedures, this method provides a means of determining thifensulfuron methyl in kernels with a detection limit of 20 ppb (20 ng/g), based on a 25-gram sample, and 50 ppm (50 ng/g) based on a 10 gram sample for green forage and whole ears. For determination of thifensulfuron methyl residues in corn processed fractions (processed corn oil and processed corn meal), the method uses HPLC with UV detection at 254 nm. This method provides a means to determine thifensulfuron methyl at levels as low as 0.02 ppm, based on a 10 gram sample.

Thifensulfuron methyl residues in canola and flax samples were determined by an analytical method based on the use of liquid chromatography with eluent and column switching with photometric detection at 254 nm at levels as low as 0.02 ppm (limit of quantitation) using a 5 gram sample.

Residues in cotton seed and gin trash were determined based on the use of column-switching liquid chromatography with detection via positive ion electrospray mass spectroscopy. The limit of quantitation was determined to be 20 ng/g and the limit of detection was estimated to be 6 ng/g, based on a 5 gram sample.

Residues in rice commodities, and in grain sorghum forage and stover, were determined with an analytical method utilizing sample extraction by homogenization in a potassium phosphate buffer solution. The extracts were cleaned-up and concentrated by solid-phase extraction. Analysis was performed by reversed-phase HPLC and quantitatively analyzed by tandem mass spectrometric detection. The target limit of quantitation (LOQ) was 0.05 ppm for these commodities.

Thifensulfuron methyl residues in grain sorghum grain were determined by an analytical method utilizing LC/MS/MS analysis. The analytes were resolved by HPLC chromatography and

quantitatively analyzed by tandem mass spectrometric detection. The LOQ was 0.05 ppm for grain sorghum grain.

3. Magnitude of Residue

a. Wheat and Barley Grain and Straw

Field tests were conducted on wheat and barley. Residues of thifensulfuron methyl were determined in wheat and barley (grain and straw) after single postemergence applications of thifensulfuron methyl at rates of 0 - 4 oz ai/acre in wheat and 0 - 2 oz ai/acre in barley. The PHI was 41-140 days for the wheat grain and straw samples, 49-116 days for barley grain, and 60-89 days for barley straw. No quantifiable residues (i.e., all less than 0.02 ppm for grain or 0.05 ppm for straw) were found in any samples at normal harvest.

In separate studies, wheat was treated with thifensulfuron methyl at a rate of 0.5 oz. ai/acre or higher, and harvested at PHIs ranging from 25-42 days. No thifensulfuron methyl residues were detected in wheat grain or straw (i.e., all less than 0.02 ppm or 0.05 ppm, respectively) in any of the trials at normal harvest. Barley was treated with thifensulfuron methyl at a rate of 0.5 oz. ai/acre. Samples of mature barley grain and straw were taken from the test plots at a PHI of approximately 40 days after the test substance was applied. All results were below 0.05 ppm for grain and 0.1 ppm for straw.

The current tolerance for thifensulfuron methyl on wheat and barley grain is 0.05 ppm, and on wheat and barley straw the tolerance is 0.1 ppm.

b. Corn Grain, Forage and Fodder

Field tests were conducted at sites representative of the major U.S. corn growing regions. Tests included two decline studies. Residues of thifensulfuron methyl were determined in corn grain, forage, and fodder after a single postemergent application of thifensulfuron methyl at rates from 0 to 1 oz ai/acre. PHIs were 80-154 days for the grain sample, 0-97 days for forage, and 82-154 days for fodder. No residues above the quantitation limit (0.02 mg/kg for grain, 0.05 mg/kg for forage/fodder) were found in any grain or fodder samples at normal harvest. Residues in forage declined very rapidly with time. Even with treatment at several times the typical use rate, residues were below the limit of quantitation within 14 days after treatment. In another study, plots were treated with thifensulfuron methyl at rates of 0.5, 1.0, and 2.0 oz. ai/acre. No thifensulfuron methyl was detected (quantitation limit of 0.02 ppm) in grain from the 2.0 oz. application rate. No residues of thifensulfuron methyl were detected in the processed fractions (corn oil and corn meal).

Field tests were also conducted to determine residues of thifensulfuron methyl in field corn commodities after a pre-plant or at-planting, exaggerated rate application. The analytical method limit of quantitation (LOQ) was 0.05 ppm and the limit of detection (LOD) was 0.02 ppm. In

these exaggerated rate studies, no residues were detected at or above 0.02 ppm in corn forage, grain, or stover.

The current tolerance for thifensulfuron methyl on field corn grain is 0.05 ppm, and on field corn forage and stover the tolerance is 0.1 ppm. These tolerances are adequate to support both the current and proposed uses of thifensulfuron methyl on field corn.

c. Soybeans

A study was conducted to evaluate the magnitude of residues of thifensulfuron methyl in soybeans at either 0.125 oz. ai/acre or 0.25 oz. ai/acre. All applications were made approximately 60 days before harvest and were postemergence foliar broadcast treatments. All thifensulfuron methyl residues in treated soybeans were below the limit of quantitation of 0.05 ppm at normal harvest.

Field tests were also conducted to determine residues of thifensulfuron methyl in soybean seed after a pre-plant or at-planting, exaggerated rate application. The analytical method LOQ was 0.05 ppm and the LOD was 0.02 ppm. In these exaggerated rate studies, no residues were detected at or above 0.02 ppm.

The current tolerance for thifensulfuron methyl on soybean (seed) is 0.1 ppm, and is adequate to support the both the current and proposed uses of thifensulfuron methyl.

d. Oat Grain and Straw

In a study using either 0.45 oz ai/acre or 0.90 oz ai/acre thifensulfuron methyl on oats, samples of mature oat grain and straw were taken from plots at preharvest intervals ranging from 39 to 57 days after the application of the test substance. Results show that residues of thifensulfuron methyl from 9 field tests were below the limit of detection (0.0055 ppm for oat grain, and 0.018 ppm for oat straw). Thifensulfuron methyl residues in 2 treated oat straw samples at a California test site showed residues of 0.041 and 0.30 mg/kg, which is above the LOQ of the analytical method. No detectable residues of thifensulfuron methyl were found in oat grain collected at that same site.

The current tolerance for thifensulfuron methyl on oat grain is 0.05 ppm, and on oat straw the tolerance is 0.1 ppm.

e. Canola and Flax

Magnitude of residue studies were conducted on a variety of Canola containing the “Smart”™ trait at fifteen test sites, and on CDC Triffid Flax. All treatment plots received an application at a rate of 0.2 or 0.4 oz. ai/acre as a broadcast foliar application. The canola variety containing the “Smart”™ trait ranged from cotyledon up to the 8 leaf stage at application. CDC Triffid Flax staging at application ranged from 5 to 20 cm in height. At harvest, no thifensulfuron methyl

residues were found above the limit of quantitation of 0.02 ppm in any seed samples treated with the test substance.

The current tolerance for thifensulfuron methyl on canola and flax seed is 0.02 ppm.

f. Cotton Seed and Gin Trash

Magnitude of the residue studies were conducted to determine residues of thifensulfuron methyl in cotton seed and cotton gin trash. The study consisted of three treatments. Treatment 1: One broadcast application at 0.3 oz ai/A, applied approximately 14 days prior to planting. Treatment 2: One broadcast application at 0.3 oz ai/A, applied pre-plant, on the day of planting. Treatment 3: One broadcast application at 1.5 oz ai/A (5X exaggerated use rate), applied pre-plant, the day of planting. Pre-harvest intervals (PHIs) ranged from 123 to 196 days. The experimentally determined limit of quantitation was 0.02 ppm. The limit of detection was estimated to be 0.006 ppm. No thifensulfuron methyl residues were found above the limit of quantitation of 0.02 ppm in any cotton seed and cotton gin trash samples treated with the test substance.

The current tolerance for thifensulfuron methyl on cotton seed and cotton gin by-products is 0.02 ppm.

g. Rice Grain and Straw

Studies were conducted to determine residues of thifensulfuron methyl in rice grain and straw. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of thifensulfuron methyl at a rate of 2.25 oz ai/acre, which was five times the maximum expected label rate. Rice grain and straw samples were collected at normal harvest (106 - 129 days after application) and analyzed for residues of thifensulfuron methyl. In these exaggerated rate studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

The proposed tolerance for thifensulfuron methyl on rice grain and straw is 0.05 ppm.

h. Grain Sorghum Forage, Stover and Grain

Studies were conducted to determine residues of thifensulfuron methyl in sorghum forage, stover, and grain. Two test plots were established at each site. One plot was untreated and provided control samples for analysis. The other plot received one pre-planting or at-planting application of thifensulfuron methyl at a rate of 2.25 oz ai/acre, which was five times the maximum expected label rate. Grain sorghum forage, stover, and grain samples were collected at normal harvest (87-103 days after application for forage, and 133-144 days after application for stover and grain) and analyzed for residues of thifensulfuron methyl. In these exaggerated rate studies, at normal harvest, no residues were detected (limit of detection 0.02 ppm) in any untreated control or treated samples analyzed.

The proposed tolerance for thifensulfuron methyl on grain sorghum forage, stover, and grain is 0.05 ppm.

B. Toxicological Profile

1. Acute Toxicity

Based on EPA criteria, technical thifensulfuron methyl is in acute toxicity Category IV for oral and inhalation routes of exposure, and for eye irritation. Thifensulfuron methyl is in acute toxicity Category III for the dermal route of exposure and for dermal irritation. It is not a skin sensitizer.

Acute oral toxicity in rats	LD_{50} > 5000 mg/kg
Acute dermal toxicity in rabbits	LD_{50} > 2000 mg/kg
Acute inhalation toxicity in rats	LC_{50} > 7.9 mg/L
Primary eye irritation in rabbits	Moderate irritation
Primary dermal irritation in rabbits	Slight irritation
Dermal sensitization in guinea pigs	Non-sensitizer

2. Genotoxicity

Technical thifensulfuron methyl has shown no genotoxic or mutagenic activity in the following *in vitro* and *in vivo* tests :

In vitro Mutagenicity Ames Assay	Negative
In vitro Mutagenicity CHO/HPRT Assay	Negative
In vitro Unscheduled DNA Synthesis	Negative
In vivo Micronuclei Induction (Mouse)	Negative
In vivo Bone Marrow Chromosome Aberrations (Rat)	Negative

Thifensulfuron methyl was not mutagenic, with or without metabolic activation, in an *in vitro* bacterial gene mutation assay using *Salmonella typhimurium*. Thifensulfuron methyl also was not mutagenic in the *in vitro* CHO/HPRT assay at concentrations up to 2712 mg/L (in Chinese hamster ovary cells). In cultured primary rat hepatocytes, thifensulfuron methyl was negative for the induction of unscheduled DNA synthesis up to 2712 mg/L.

An *in vivo* bone marrow micronucleus test was conducted in mice. There was no increase in micronucleated polychromatic erythrocytes (MNPCE) frequency at a dose of 5000 mg/kg. An *in vivo* chromosome aberration study was conducted on rats. This included the assessment of chromosome aberrations by metaphase analysis in bone marrow of male and female rats.

Thifensulfuron methyl did not induce cytogenic damage in bone marrow cells at a dose of 5000 mg/kg.

3. Reproductive and Developmental Toxicity

The results of a series of studies indicated that there were no reproductive, developmental or teratogenic hazards associated with the use of thifensulfuron methyl. In a 1-generation reproduction study in rats, the suggested NOEL was 7500 ppm (559 mg/kg/day males, 697 mg/kg/day females). In a rat multigeneration reproduction study, the NOEL for reproductive effects of thifensulfuron methyl in adult rats and their offspring was 2500 ppm, the highest dietary level tested. This level was based on the absence of significant compound related effects observed in this study, and is equivalent to 175-180 mg/kg/day in adult male rats and 212-244 mg/kg/day in adult female rats. There were no effects on fertility, lactation, litter size, or pup survival. Thifensulfuron methyl is not considered a reproductive toxin.

In studies conducted to evaluate developmental toxicity potential, thifensulfuron methyl was neither teratogenic nor uniquely toxic to the conceptus (i.e., not considered a developmental toxin). In the rat study, there was no evidence of maternal toxicity at the highest dose tested (800 mg/kg/day). Therefore, the maternal NOAEL is 725 mg/kg/day (analytically determined dose). The developmental NOAEL for rats was considered to be the 200 mg/kg/day dose level (analytically determined and set by EPA as 159 mg/kg/day) based on the decrease in mean fetal body weight and an increase in the incidence of small renal papillae. In the rabbit developmental toxicity study, there was slight maternal toxicity (decreased body weight gain) at a dose of 650 mg/kg/day. No significant indications of maternal toxicity were evident at the mid-dose level (200 mg/kg/day). No compound-related effects on fetal weights or the incidences of malformations or variations were seen at any dose. The maternal NOEL was the 200 mg/kg/day dose (analytically determined and set by EPA at 158 mg/kg/day) and the developmental NOEL was the 650 mg/kg/day dose level (analytically determined and set by EPA at 511 mg/kg/day) for rabbits dosed with thifensulfuron methyl by gavage on gestation days 7-19.

4. Subchronic Toxicity

The most sensitive species to subchronic exposure of thifensulfuron methyl was the rat. The NOEL for thifensulfuron methyl was 100 ppm (7 and 9 mg/kg/day) for male and female rats, respectively, in the 90-day dietary study. This was based on the decreased body weight, food efficiency, and changes in clinical chemistry in the 2500 and 7500 ppm groups. For mice in both the 4-week range-finding and the 90-day studies, the NOEL for male and female mice under the conditions of this study was 7500 ppm. This was based on the lack of compound-related effects at the highest concentration, equivalent to 1427 mg/kg/day in male mice and 2287 mg/kg/day in female mice. EPA concluded the NOEL for subchronic (90-day dietary) exposure in dogs was 1500 and 7500 ppm in males and females (equivalent to 37.5 mg/kg/day and 159.7 mg/kg/day) respectively. These levels were based on lower body weight and adrenal weight in males, and a lack of adverse effects in females at 7500 ppm, the highest concentration tested. No compound-related pathologic lesions were observed and no target organ was identified in all of the above

tests.

5. Chronic Toxicity/Oncogenicity

The NOEL for chronic (2-year dietary) exposure in rats was 500 ppm (20 mg/kg/day for males and 26 mg/kg/day for females), based on body weight effects at 2500 ppm. Thifensulfuron methyl was not an oncogen in rats.

In an 18-month study in mice, conducted at dietary levels of 0, 25, 750, and 7500 ppm, EPA concluded the NOEL was 25 ppm (4.3 mg/kg/day) based on decreased body weight gains in female mice at 750 ppm and above, and in male mice at 7500 ppm. No other effects were observed in the study. Thifensulfuron methyl was not an oncogen in mice.

In a 1- year feeding study in dogs, the NOEL of thifensulfuron methyl was 750 ppm in male and female beagle dogs (equivalent to approximately 18.75 mg/kg/day), based on decreased body weights, body weight gains, and food efficiency in females and increased liver weights in males, all at 7500 ppm. The liver weight effects in males in the absence of other effects including histopathology may be adaptive rather than adverse.

6. Animal Metabolism

The metabolic pathway for thifensulfuron methyl in animals is understood. This metabolic pathway involves hydrolysis of the urea bridge, deesterification, and O-demethylation reactions. There was minimal potential for retention or accumulation of thifensulfuron methyl or its metabolites in animal tissues. Low levels of thifensulfuron methyl residues were found in goat tissues and insignificant tissue levels (i.e., less than 0.1% of the dose) were observed in the rat.

Rats were dosed with two radioactive forms of thifensulfuron methyl (^{14}C-thiophene and ^{14}C-triazine). In the thiophene study, the thifensulfuron methyl was primarily excreted unchanged by rats following low dose (20 mg/kg), low dose following 21 days dietary preconditioning (100 ppm), and high dose (2,000 mg/kg) routines. Approximately 70% to 85% of the excreted radioactivity was thifensulfuron methyl. The urine was the primary excretion route and contained 71% to 92% of the original dose from the low and low-dose preconditioned groups. Combined urinary and fecal elimination was rapid, with over 90% of excretion completed by 48 hours after dosing for both low-dose groups. The high-dose group peak elimination was delayed by approximately 24 hours compared to the other dose levels. Tissue radioactivity levels were low at sacrifice (96 hours after dosing) for all dosing groups, with no enhanced retention of radioactivity by any organ or tissue. Thifensulfuron methyl was the primary radiolabeled excretion product with thifensulfuron acid, 2-acid-3-sulfonamide, 2-ester-3-sulfonamide, and thiophene sulfonamide identified as minor metabolites.

In the triazine study, thifensulfuron methyl was excreted primarily unchanged in urine and feces by male and female rats after administration of approximately 2000 mg/kg by oral gavage. Urine was the primary route of excretion, averaging 58.7% of the dose in males and 75.5% in females. Fecal

excretion of the dose averaged 21.2% for the male rats and 15.8% for the females. Greater than 50% of the dose was excreted by 48 hours post-dosing. Essentially no elimination of the dose as radiolabeled CO_2 or volatile compounds occurred. These results are similar to those reported on the thiophene-labeled thifensulfuron methyl. Intact thifensulfuron methyl was identified by mass spectrometry as the principal radioactive compound in urine (> 94%) and feces (> 77%). Three minor metabolites, each less than 3% of the dose, were identified in urine and feces by chromatographic retention comparison; they were thifensulfuron acid, O-demethyl thifensulfuron methyl, and triazine amine.

Results from a metabolism study with two radioactive forms of thifensulfuron methyl (^{14}C-triazine and ^{14}C-thiophene) in lactating goats show that most of the dosed radioactivity was rapidly excreted (primarily in the urine) and recovered as intact thifensulfuron methyl. Radioactivity in the milk (0.1 - 0.2 ppm) was comprised of mostly intact thifensulfuron methyl and a small amount of triazine amine and several very minor metabolites. Radioactivity did not accumulate in the tissues. After absorption, the major metabolic pathway involved cleavage of the carboxyl ester linkage, resulting in the formation of thifensulfuron acid. Oxidative O-demethylation occurred to a limited extent.

There were no significant levels of unique plant metabolites of thifensulfuron methyl found in food or feed products at crop maturity. Hence, toxicity testing of other degradation products of thifensulfuron methyl is not needed.

7. Metabolite Toxicology

There is no evidence that the metabolites of thifensulfuron methyl, as identified in either the plant or animal metabolism studies, are of any toxicological significance.

8. Endocrine Effects

No special studies investigating potential estrogenic or other endocrine effects of thifensulfuron methyl have been conducted. However, the standard battery of required toxicology studies has been completed. These include an evaluation of the potential effects on reproduction and development, and an evaluation of the pathology of the endocrine organs following repeated or long-term exposure to doses that far exceed likely human exposures. Based on these studies, there is no evidence to suggest that thifensulfuron methyl has an adverse effect on the endocrine system.

C. Aggregate Exposure

Thifensulfuron methyl is the active ingredient in a number of DuPont herbicides, with new uses being proposed for pre-plant or at-planting herbicidal treatment for soybeans, field corn, rice, and sorghum. There are no residential uses for any thifensulfuron methyl containing herbicides.

1. Dietary Exposure

The chronic reference dose (cRfD) of 0.2 mg/kg/day is based on the NOEL of 20 mg/kg/day from a two-year rat feeding study and a 100X safety factor. The acute reference dose (aRfD) of 1.59 mg/kg/day is based the NOEL of 159 mg/kg/day from a rat developmental study and a 100X safety factor.

The residue of concern, as listed at 40 CFR 180.439, is parent thifensulfuron methyl only.

2. Food

a. Chronic Dietary Exposure Assessment

Dietary exposure, resulting from the current and proposed uses of thifensulfuron methyl on barley, canola, cotton, flax, field corn, oats, soybeans, sorghum, rice and wheat, is well within the acceptable limits for all sectors of the population, as predicted by both the Chronic and Acute Modules of the Dietary Exposure Evaluation Model (DEEM, Exponent, Inc., 2003 Version 7.87). The percentage or proportion of a crop that is treated can have a significant effect on the exposure profile. In this case, it was assumed for all crops that 100% was treated with thifensulfuron methyl. Based on a comparison with the actual use profiles for herbicides containing thifensulfuron methyl, this is an extremely conservative estimate.

The predicted chronic exposure for the U.S. population subgroup was 0.0000151 mg/kg bw/day. The population subgroup with the highest predicted level of chronic exposure was the non-nursing infants subgroup with an exposure of 0.0000401 mg/kg bw/day. Based on a chronic NOEL of 20 mg/kg bw/day and a 100-fold safety factor, the cRfD would be 0.2 mg/kg bw/day. For the U.S. population, the predicted exposure is equivalent to less than 1% of the cRfD. For the population subgroup with the highest level of exposure (non-nursing infants), the exposure would also be equivalent to less than 1% of the cRfD. Because the predicted exposures, expressed as percentages of the cRfD, are well below 100%, there is reasonable certainty that no chronic effects would result from dietary exposure to thifensulfuron methyl.

b. Acute Dietary Exposure

The predicted acute exposure for the U.S. population subgroup was 0.000595 mg/kg bw/day (95^{th} percentile). The population subgroup with the highest predicted level of acute exposure was the non-nursing infants subgroup with an exposure of 0.001437 mg/kg bw/day (95^{th} percentile). Based on an acute NOEL of 159 mg/kg bw/day and a 100-fold safety factor, the aRfD would be 1.59 mg/kg bw/day. For the U.S. population the predicted exposure (at the 95^{th} percentile) is equivalent to 0.04% of the aRfD. For the population subgroup with the highest level of exposure (non-nursing infants subgroup), the exposure (at the 95^{th} percentile) would be equivalent to 0.09% of the aRfD. Because the predicted exposures, expressed as percentages of the aRfD, are well below 100%, there is reasonable certainty that no acute effects would result from dietary exposure to thifensulfuron methyl.

3. Drinking Water

Surface water exposure was estimated using the Generic Expected Environmental Concentration (GENEEC) model. Groundwater exposures were estimated using SCI-GROW.

The EPA uses drinking water levels of comparison (DWLOCs) as a surrogate measure to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper limit in light of total aggregate exposure to that pesticide from food, water, and residential uses. A DWLOC will vary depending on the residue level in foods, the toxicity endpoint, and with drinking water consumption patterns and body weights for specific subpopulations.

The acute DWLOCs are 56 ppm (parts per million) for adult males, 48 ppm for adult females, and 16 ppm for the subpopulation with the highest exposure (non-nursing infants). The estimated maximum concentration of thifensulfuron methyl in surface water (1.2 parts per billion, or ppb) derived from GENEEC is much lower than the acute DWLOCs. Therefore, one can conclude with reasonable certainty that residues of thifensulfuron methyl in drinking water do not contribute significantly to the aggregate acute human health risk.

The chronic DWLOCs are 0.45 ppm for adult males, 0.38 ppm for adult females, and 0.12 ppm for the subpopulation with the highest exposure (non-nursing infants). These DWLOC values are substantially higher than the GENEEC 56-day estimated environmental concentration of 0.65 ppb for thifensulfuron methyl in surface water. Therefore, one can conclude with reasonable certainty that residues of thifensulfuron methyl in drinking water do not contribute significantly to the aggregate chronic human health risk.

4. Non-Dietary Exposure

Thifensulfuron methyl is not registered for any use which could result in non-occupational or non-dietary exposure to the general population.

D. Cumulative Effects

Thifensulfuron methyl belongs to the sulfonylurea class of crop protection chemicals. Other structurally similar compounds in this class are registered as herbicides. However, the herbicidal activity of sulfonylureas is due to the inhibition of acetolactate synthase (ALS), an enzyme found only in plants. This enzyme is part of the biosynthesis pathway leading to the formation of branched chain amino acids. Animals lack ALS and this biosynthetic pathway. This lack of ALS contributes to the relatively low toxicity of sulfonylurea herbicides in animals. There is no reliable information that would indicate or suggest that thifensulfuron methyl has any toxic effects on mammals that would be cumulative with those of any other chemical.

E. Safety Determination

Based on data and information submitted by DuPont, EPA previously determined that the establishment of tolerances of thifensulfuron methyl on the barley, oats, wheat, field corn, cotton, canola, flax, and soybean raw agricultural commodities would protect the public health, including the health of infants and children.

Establishment of new tolerances for thifensulfuron methyl on Rice grain at 0.05 ppm, Rice straw at 0.05 ppm, Grain sorghum grain at 0.05 ppm, Grain sorghum forage at 0.05 ppm, and Grain sorghum stover at 0.05 ppm will also not adversely impact public health.

1. U.S. Population

Based on the completeness and reliability of the toxicology database, and using the conservative assumptions presented earlier, EPA has established a cRfD of 0.2 mg/kg/day. This was based on the NOEL for the chronic rat study, 20 mg/kg/day, and a 100-fold safety factor. It has been concluded that the chronic dietary exposure was less than 1% of the cRfD. Generally, exposures below 100% of the cRfD are of no concern because it represents the level at or below which daily dietary exposure over a lifetime will not pose appreciable risk to human health. Thus, there is reasonable certainty that no harm will result from chronic exposures to thifensulfuron methyl residues.

2. Infants and Children

In assessing the potential for additional sensitivity of infants and children to residues of thifensulfuron methyl, data from the previously discussed developmental and multigeneration reproductive toxicity studies were considered.

Developmental studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during pre-natal development. Reproduction studies provide information relating to reproductive and other effects on adults and offspring from pre-natal and post-natal exposures to the pesticide. The studies with thifensulfuron methyl demonstrated no evidence of developmental toxicity at exposures below those causing maternal toxicity. This indicates that developing animals are not more sensitive to the effects of thifensulfuron methyl administration than adults.

FFDCA section 408 provides that EPA may apply an additional uncertainty factor for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the database. Based on current toxicological data requirements, the database for thifensulfuron methyl relative to pre- and post-natal effects for children is complete. In addition, the NOEL of 20 mg/kg/day in the chronic rat study (and upon which the RfD is based) is much lower than the NOELs defined in the reproduction and developmental toxicology studies. The sub-population with the highest level of exposure was Non-Nursing Infants (< 1 yr), where exposure was less than 1% of the cRfD. Based on these conservative analyses, there is reasonable certainty that no harm will result to infants and children from aggregate exposures to thifensulfuron methyl.

F. International Tolerances

The maximum residue limit (MRL) in Canada for thifensulfuron methyl on canola is 0.1 ppm. The MRLs in the EU (European Union) are 0.05 ppm for barley, field corn (maize), oats, soybeans (soya bean), wheat, canola (rapeseed), cotton seed, flax (other oilseeds), rice, sunflowers, and sorghum.

(FR Notice – Thifensulfuron, Draft 1. December 6, 2004)